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L5	L2 and basic	49	L5
L4	L2 and anionic	28	L4
L3	L2 and carrageenan	13	L3
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- Crauste-Manciet, S.; Huneau, J.F.; Decroix, M.O.; Tomé, D.; Farinotti, R.; Chaumeil, J.C., pp. 241-249, Article Full-text PDF (624 KB)
  Score: **100**, April 28, 1997

Cefpodoxime screening of *Escherichia coli* and *Klebsiella* spp. by Vitek for detection of organisms producing extended-spectrum β-lactamases *(Diagnostic Microbiology and Infectious Disease, Volume: 38, Issue: 4)*

- Gibb, A. Patrick; Crichton, Marilyn, pp. 255-257, Article Full-text PDF (48.1 KB)
  Score: **76**, December 2000

Cefpodoxime-proxetil protection from intestinal lumen hydrolysis by oil-in-water submicron emulsions *(International Journal of Pharmaceutics, Volume: 165, Issue: 1)*

- Crauste-Manciet, Sylvie; Brossard, Denis; Decroix, Marie-Odile; Farinotti, Robert; Chaumeil, Jean-Claude, pp. 97-106, Article Full-text PDF (148 KB)
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- Fuchs, Peter C.; Barry, Arthur L.; Brown, Steven D., pp. 281-287,
  Article Full-text PDF (138 KB)
  Score: **37**, December 1998

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  Article Full-text PDF (283 KB)
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  Score: **18**, July 1995

Antimicrobial Resistance Issues of the Future *(Diagnostic Microbiology and Infectious Disease, Volume: 25, Issue: 4)*

- Craig, William A., pp. 213-217, Article Full-text PDF (467 KB)
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In Vitro Activity of Oral Antimicrobial Agents Against Clinical Isolates of Pasteurella multocida *(Diagnostic Microbiology and Infectious Disease, Volume: 30, Issue: 2)*

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  Article Full-text PDF (323 KB)
  Score: **16**, February 1998

A 1994-95 Survey of Haemophilus influenzae Susceptibility to Ten Orally Administered Agents: A 187 Clinical Laboratory Center Sample in the United States *(Diagnostic Microbiology and Infectious Disease, Volume: 27, Issue: 3)*

- Jones, Ronald N.; Jacobs, Michael R.; Washington, John A.; Pfaller, Michael A., pp. 75-83, Article Full-text PDF (795 KB)
  Score: **12**, March 1997

Identification and Natural Antibiotic Susceptibility of *Morganella morganii* *(Diagnostic Microbiology and Infectious Disease, Volume: 30, Issue: 3)*

- Stock, Ingo; Wiedemann, Bernd, pp. 153-165, Article Full-text PDF (890 KB)
  Score: **11**, March 1998

Comparative In Vitro Assessment of Sparfloxacin Activity and Spectrum Using Results from Over 14,000 Pathogens Isolated at 190 Medical Centers in the USA *(Diagnostic Microbiology and Infectious Disease, Volume: 29, Issue: 3)*

- Ballow, Charles H.; Jones, Ronald N.; Johnson, David M.; Deinhart, June A.; Schentag, Jerome J., pp. 173-186, Article Full-text PDF (1.41 MB)
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  Score: **9**, May 1998

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* NOTICES *

CLAIMS

[Claim(s)]

[Claim 1] The physic constituent which prevented the unpleasant taste obtained by mixing the wax-like matter of the water soluble polymer of a medicine, one sort, or several sorts which has the unpleasant taste of one sort or several sorts and one sort, or several sorts.

[Claim 2] The physic constituent which prevented the unpleasant taste according to claim 1 which mixes the wax-like matter of the water soluble polymer of a medicine, one sort, or several sorts which has the unpleasant taste of one sort or several sorts and one sort, or several sorts, heats, carries out the granulation of the wax-like matter and water soluble polymer which were dissolved together, and is obtained.

[Claim 3] The physic constituent with which the water soluble polymer prevented the unpleasant taste according to claim 1 chosen from a cellulose system macromolecule, gelatin, casein, or the carrageenin.

[Claim 4] The physic constituent with which the wax-like matter prevented the unpleasant taste according to claim 1 chosen from higher alcohol, a higher fatty acid, hardened oil, a vegetable property, animal fat, or a cane-sugar fatty acid.

[Claim 5] The physic constituent with which the water soluble polymer prevented one or the unpleasant taste according to claim 1 chosen two or more out of the hydroxypropyl methylcellulose, hydroxypropylcellulose, a hydroxyethyl cellulose, carboxymethylcellulose sodium, a polyvinyl pyrrolidone, a methyl cellulose, gelatin, the carrageenin, and casein.

[Claim 6] The physic constituent with which the wax-like matter prevented one or the unpleasant taste according to claim 1 chosen two or more from a stearyl alcohol, a cetanol, stearin acid, a palmitic acid, hardening castor oil, hardening rapeseed oil, hardening cotton seed oil, a carnauba wax, white beeswax, and sucrose fatty acid ester.

[Claim 7] The physic constituent which prevented the unpleasant taste according to claim 1 whose content of a medicine is 50 or less % of the weight.

[Claim 8] The physic constituent which prevented the unpleasant taste according to claim 1 whose content of a water soluble polymer is 5 - 60 % of the weight.

[Claim 9] The physic constituent with which the wax-like matter prevented the unpleasant taste according to claim 1 which is 10 - 90 % of the weight.

[Claim 10] The granule which comes to use a constituent according to claim 1, powder, dry syrup, a tablet, a capsule.

[Claim 11] The manufacture technique of the physic constituent which mixed the wax-like matter water soluble polymer of the water soluble polymer of the medicine of one sort or several sorts, one sort, or several sorts and one sort, or several sorts, heated, and prevented the unpleasant taste according to claim 1 which carries out the granulation of the dissolved wax-like matter with a medicine and a water soluble polymer.

[Claim 12] The manufacture technique of the granule and powder using the physic constituent according to claim 1, dry syrup, a tablet, and a capsule.

[Claim 13] a medicine -- 7beta-[2-(2-aminothiazole-4-****)-2 -(Z)-hydroxyimino acetamide]-3-N and N-dimethyl carbamoyl oxymethyl-3-cephem-carboxylic acid 1-(isopropoxycarbonyloxy) ethyl ester The physic constituent which prevented the unpleasant taste of the claim 1 which is a hydrochloride, the claim 10, the claim 11, or the claim 12 given in any one term, tablets, or such manufacture technique.

[Claim 14] A medicine The medicine of one sort or several sorts, One sort Or the water soluble polymer of several sorts And the physic constituent which prevented the unpleasant taste of the claim 1 which is a (E)-3-(2-methoxy -3, 6-dimethyl-1, 4-benzoquinone-5-****)-2-[5-(3-pyridyl) pentyl]-2-propene acid, the claim 10, the claim 11, or the claim 12 given in any one term, Tablets or such manufacture technique.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] this invention relates to the physic constituent which prevents the unpleasant taste of a physic compound, a tablet, and its manufacture technique. Furthermore, it is related with the physic constituent which prevented in detail the unpleasant taste which comes to contain a water soluble polymer and the wax-like matter, tablets, or such manufacture technique.

[0002]
[The background and the conventional technique] of invention Trouble will be caused to obtaining the effect of a medicine for the maximum -- a patient's compliance falls -- if there is an unpleasant taste when carrying out internal use of the medicine, although restricted to neither a child nor old people. Then, making it dosage forms, such as a sugar-coated pill, a film coat lock, and a capsule, and covering and carrying out internal use of the unpleasant taste has been performed from the former. However, it is hard to carry out the deglutition of such a tablet, and is hard to medicate a child and old people with it too. Then, the tablet which covered the unpleasant taste has been strongly desired by the dosage forms which are easy to carry out a deglutition, such as powder and a granule.
[0003] Although a tablet device, such as adding a sweetening agent and perfume, was made in order to suppress the unpleasant taste in the inside of the opening at the time of recipe of powder, a granule, etc. now, suppression of the perfect unpleasant taste was difficult.
[0004] then, although the technique of carrying out the pulverization by the spray ******** method after sharing with the technique or the wax-like matter coated with the microencapsulation of a physic compound and a stomach solubility base material is taken, equipment special to a manufacture in the biological utilization factor of a physic compound falling is required just because it makes masking perfect -- etc. -- it has the fault Moreover, after corning a physic compound and the mixture of the water bloating tendency matter with dry process, the covering tablet which **ed so that the wax-like matter might wear a front face and which carried out bitterness masking is indicated by JP,4-300821,A. However, by this technique, prevention of bitterness was inadequate, and since it was necessary to heat-treat after a granulation and to coat the wax-like matter, there was a fault without the good operability at the time of being a manufacture.
[0005]
[Problem(s) to be Solved by the Invention] From the above statuses, it still craves for the tablet which a child, old people, etc. tend to take and which covered the unpleasant taste. Then, this invention person etc. is the constituent which covered the unpleasant taste, tended to do a deglutition also in a child or old people, and started the research zealously that it is the constituent which can obtain tablets, such as a good granule of elution, and dry syrup, easily, and should search for such a constituent or the good manufacture technique of the operability of a tablet.
[0006]
[Means for Solving the Problem] Consequently, the physic constituent shown below and its manufacture technique found out attaining the desired end, and this invention person etc. completed this invention.
[0007] Namely, the physic constituent which prevented the unpleasant taste obtained when this invention mixes the wax-like matter of the water soluble polymer of a medicine, one sort, or several sorts which has the unpleasant taste of one sort or several sorts and one sort, or several sorts, The granule which comes out, exists and comes to use this physic constituent, powder, dry syrup; Come out, and are and the wax-like matter water soluble polymer of the water-soluble polymer of the medicine of one sort or several sorts, one sort, or several sorts and one sort, or several sorts is mixed. a tablet and a capsule -- the manufacture technique of the physic constituent which prevented the unpleasant taste according to claim 1 which heats and carries out the granulation of the dissolved wax-like matter with a medicine and a water-soluble polymer -- it comes out
[0008] In this invention, although the unpleasant taste sensed as the unpleasant taste when a recipe person contains this physic compound in the opening, for example, bitterness, an astringent taste, a pungent condiment, ******, etc. are natural, when contained in the opening, the displeasure of which it complains also to the olfaction which has close relation in the gustation is also included.
[0009] As an example of the medicine with these unpleasant tastes, hydrochloric-acid **********, hydrochloric-acid **********, 7beta-[2-(2-aminothiazole-4-****)-2 -(Z)-hydroxyimino acetamide]-3-N and N-dimethyl carbamoyl oxymethyl-3-cephem-carboxylic acid 1-(isopropoxycarbonyloxy) ethyl ester Hydrochloride, (E) -3-(2-methoxy -3, 6-dimethyl-1, 4-benzoquinone-5-****)-2-[5-(3-pyridyl) pentyl]-2-propene acid, A chlorination berberine, a digitoxin, a sulpyrine, the etilefrine

hydrochloride, diltiazem hydrochloride, Although the propranolol hydrochloride, a chloramphenicol, an aminophylline, an erythromycin, a phenobarbital, a calcium pantothenate, hydrochloric-acid indie **********, a hydrochloric-acid aminoguanidine, etc. can be raised, it is not limited to these.

[0010] Although anything is sufficient as the wax-like matter said by this invention as long as it may fuse by heating, it can illustrate the sucrose fatty acid ester which can come to hand with tradenames, such as vegetable properties, such as hardened-oil; carnauba waxes, such as higher-fatty-acid; hydrogenated castor oil, such as higher-alcohol; stearin acid, such as a stearyl alcohol and a cetanol, and a palmitic acid, the hardening rapeseed oil, and hardening cotton seed oil, and white beeswax, or animal fat; ********** sugar fatty acid ester S-370, and ********** sugar fatty acid ester S-570. About 40 - 90 degrees C of abbreviation, still preferably, the desirable melting points of the wax-like matter are about 60 - 85 degrees C of abbreviation, and can choose the wax-like matter to which tinction and disassembly of a medicine seldom happen by contact of the shape of a medicine and a wax.

[0011] If the water soluble polymer said by this invention is matter which becomes gel-like, and is melted or distributed with still a lot of water with little water, it is good anything. If an example is given, although macromolecules, such as cellulose system macromolecules, such as a hydroxymethyl cellulose, the hydroxypropyl methylcellulose, a hydroxyethyl cellulose, carboxymethylcellulose sodium, and a methyl cellulose, a polyvinyl pyrrolidone, gelatin, the carrageenin, and casein, can be raised, it is not limited to these. By contact to a medicine, the water soluble polymer to which tinction and disassembly of a medicine seldom happen can be chosen.

[0012] this invention -- the desirable compounding ratio of such a constituent -- about 50 or less % of the weight, and wax-like matter about 10- -- about 90 % of the weight and water-soluble-polymer about 5- -- although it is about 60% -- further -- desirable -- about 50 or less % of the weight of medicines, the wax-like matter 20, - about 60% % of the weight and water-soluble-polymer about 20 -- about 50% -- further -- desirable -- 50 or less % of the weight, and wax-like matter about 30- -- about 50 % of the weight and water-soluble-polymer about 20- -- it is about

[0013] A wax dissolves the physic constituent used by this invention, and if it is technique by which a granulation is carried out with a medicine and a water soluble polymer, it can be obtained by every technique. For example, a medicine, the wax-like matter, and a water soluble polymer are supplied to revolution fluidized bed granulators (spa ****** flow etc.), and are warmed, after fusing a wax, it can stir, the technique of carrying out a granulation, a medicine, the wax-like matter, and a water soluble polymer can be stirred after warming and fusion in a container, and the technique of carrying out the granulation of this fusion mixture by spray ******** using spray dry, the technique of carrying out a stirring granulation using high-speed stirring granulating machines (super mixer etc.) Every model can use a revolution fluidized bed granulator, a high-speed stirring granulating machine, etc. which are used conventionally.

[0014] Although it can also be used as a tablet as it is, such a constituent can also be used for this invention as tablets, such as powder and a granule, even if it carries out a particle size regulation using particle-size-regulation machines, such as a speed mill. About the constituent which performs a particle size regulation and was obtained, you may heat-treat by using a fluidized-bed-drying machine further in order to raise suppression of the unpleasant taste. Moreover, after manufacturing this constituent in consideration of recipe nature, saccharides, such as a lactose, a mannite, a sucrose, and a powder reduction maltose starch syrup, add an excipient, it carries out a granulation by the binder, and they are good also as a tablet. Furthermore, of course, using such a constituent for this invention as it is, and considering as dry syrup, a tablet, or a capsule by the conventional method is also included by this invention. An example is hung up in order to make understanding of this invention easy below.

[0015]

[Example]

Example 1 [0016] 7beta-[2-(2-aminothiazole-4-****)-2 -(Z)-hydroxyimino acetamide]-3-N and N-dimethyl carbamoyl oxymethyl-3-cephem-carboxylic acid 1-(isopropoxycarbonyloxy) ethyl ester Hydrochloride (it is indicated as a medicine 1 below) 4.5g carboxymethylcellulose sodium 1.5g hydrogenated castor oil 12.0g [0017] Three kinds of components were mixed with the small stirring granulating machine. The granulation container was succeedingly heated at the heater and it stirred in the place which the wax-like matter began to dissolve. When the granulation was completed, the granulation container was cooled, the sieving of the granulation object was carried out, and granulatio 500 micrometers or less was obtained.

[0018] The constituent by the following prescription was obtained according to the technique of example 2 - example 13 example 1.

[0019] Example 2 medicine 1 4.5g carboxymethylcellulose sodium 1.5g stearin acid 12.0g [0020] Example 3 medicine 1 7.5g carboxymethylcellulose sodium 2.5g hardening castor oil 10.0g [0021] Example 4 medicine 1 6.0g carboxymethylcellulose sodium 2.0g stearin acid 8.0g [0022] Example 5 medicine 1 3.0g carboxymethylcellulose sodium 3.0g stearin acid 6.0g [0023] Example 6 medicine 1 3.0g carboxymethylcellulose sodium 2.0g stearin acid 7.0g [0024] Example 7 medicine 1 4.5g carboxymethylcellulose sodium 3.0g hardening castor oil 3.8g [0025] Example 8 medicine 1 4.5g carboxymethylcellulose sodium 4.5g hardening castor oil 4.2g [0026] Example 9 medicine 1 4.5g carboxymethylcellulose sodium 1.5g hardening castor oil 3.5g [0027] Example 10(E)-3-(2-methoxy -3, 6-dimethyl-1, 4-benzoquinone-5-****)-2-[5-(3-pyridyl) pentyl]-2-propene acid (it is indicated as a medicine 2 below.) 4.0g hydroxypropylcellulose 4.0g hardening castor oil 4.0g [0028] Example 11 medicine 2 4.0g hydroxypropylcellulose 4.0g hardening castor oil 4.0g [0029] The power mill (500 micrometers of the scale-division vacancies of the screen) performed the particle size regulation for the constituent obtained in the example 12 example 8, and the granule was obtained.

[0030] The granule obtained in the example 13 example 12 was made to flow for 15 minutes at 90 degrees C (charge air temperature) with a fluidized-bed-drying machine, and the granule was obtained.

[0031] Example 14 medicine 2 4.0g carboxymethylcellulose sodium 4.0g hardening castor oil 4.0g [0032] According to the technique of an example 1, it classified further and the granule 500 micrometers or less was obtained.
[0033]
[Effect of the Invention] Since the effect of this invention is shown below, the example of an experiment is hung up.
the example 1 of an experiment -- unpleasant -- taste prevention effect (1)7beta-[2-(2-aminothiazole-4-****)-2 -(Z)-hydroxyimino acetamide]-3-N and N-dimethyl carbamoyl oxymethyl-3-cephem-carboxylic acid 1-(isopropoxycarbonyloxy) ethyl ester The unpleasant taste (bitterness) prevention effect of a hydrochloride (medicine 1) was examined by the following technique. the place which preceded the exam first, performed the organoleptics of the taste as a preliminary test, and calculated the threshold of bitterness -- about 20microg/ml it was -- from things, when the following exams were also below this concentration, it was judged that there was no bitterness
[0034] (1) The constituent obtained in the example 1 of 50mg considerable amount of the experiment technique medicine 1 - the example 9 was added to 30ml of water, and was shaken by the hand for 10 seconds, it filtered immediately in Millipore (0.45 micrometers), 1ml of this filtrate was diluted with the decinormal hydrochloric acid to 5ml, and determination was performed by HPLC. Based on this result, the concentration of the medicine 1 eluted in the filtrate was calculated. When this concentration was 20micro less thang/ml, although the tablet was included in the opening, it was judged that there was no bitterness. As a contrast, the water bloating tendency matter was used instead of the water soluble polymer, and the granule obtained by the following technique was used.
[0035] (Contrast 1) 20l. super mixer was performed 338g of 484g and light anhydrous silicic acid of a medicine 1, and the granulation was performed by ethanol after mixture for 5 minutes. This was performed at 50 degrees C and the stack type dryer performed the particle size regulation on the 24 mesh screen after xeransis. ********** sugar fatty-acid-ester S-370 (tradename) 11.5g was mixed with 11.5g of this granulatio with the small stirring granulating machine. A granulation container is succeedingly heated at a heater and it stirs in the place which the wax-like matter began to dissolve. When the granulation was completed, the granulation container was cooled, the sieving of the granulation object was carried out, and granulatio 1000 micrometers or less was obtained.
[0036] (Contrast 2) ********** sugar ester S-570 (tradename) was used instead of ********** sugar fatty acid ester S-370, and granulatio was obtained according to the contrast 1.
[0037] (2) An experimental-result experimental result is shown in the following table 1.
[0038]
[Table 1]

実施例No.	1	2	3	4	5
濾液中薬物濃度 (μg/ml)	2.34	7.12	1.88	11.41	7.19

実施例No.	6	7	8	9	12
濾液中薬物濃度 (μg/ml)	3.12	5.62	3.31	7.21	8.28

実施例No.	対照1	対照2
濾液中薬物濃度 (μg/ml)	245.4	459.3

[0039] The tablet of 50mg considerable amount of the example of experiment 2 elution-test (1) (1) experiment technique medicine 1 was added to 40ml of decinormal hydrochloric acids, and it shook with the shaker (200rpm) for 15 minutes, and filtered immediately in Millipore (0.45 micrometers), 1ml of this filtrate was diluted with the decinormal hydrochloric acid to 10ml, and determination was performed by HPLC. The concentration of a medicine 1 eluted in the filtrate on the basis of this result was calculated.
[0040] (2) The result of the experimental-result above is shown in Table 2.
[0041]
[Table 2]

実施例No.	1	2	3	4	5
溶出率 (%)	12	91	73	106	99

実施例No.	6	7	8	9
溶出率 (%)	95	107	103	103

[0042] The bitterness prevention effect of the example of experiment 3 unpleasant taste prevention effect (2) medicine 2 was examined by the following technique. the place which preceded the exam first, performed the organoleptics of the taste as a preliminary test, and calculated the threshold of bitterness -- about 250microg/ml it was -- from things, when the following exams were also below this concentration, it was judged that there was no bitterness

[0043] (1) The constituent of 50mg considerable amount of the medicine 2 which reaches experiment technique example 10-11 and was obtained by 14 was added to 30ml of water, and it shook with the shaker (a part for 200 times/) for 30 seconds, and filtered immediately in Millipore (0.45micro meter), and determination was performed for this filtrate by HPLC. When this concentration was 250micro less thang/ml, although the tablet was included in the opening, it was judged that there was no bitterness.

[0044] (2) The experimental result of the experimental-result above is shown in the following table 3.

[0045]

[Table 3]

実施例No.	10	11	13	14
濾液中薬物濃度 (μg/ml)	13.0	12.0	6.39	64.0

[0046] The constituent of 50mg considerable amount of the example of experiment 4 elution test (2) medicine 2 was added to 40ml of decinormal hydrochloric acids, and it shook with the shaker (200rpm) for 15 minutes, and filtered immediately in Millipore (0.45 micrometers), 1ml of this filtrate was diluted with 4ml of decinormal hydrochloric acids, and determination was performed by HPLC. The concentration of the medicine 2 eluted in the filtrate based on this result was calculated.

[0047] (2) The result of the experimental-result above is shown in Table 4.

[0048]

[Table 4]

実施例No.	10	11	14
溶出率 (%)	95	83	78

[0049] In the tablet obtained in the example of experiment 5 elution test (3) examples 7-9, the elution test was performed according to technique given in the Pharmacopoea of Japan as follows.

(1) **** correctly the tablet of 150mg considerable amount of the experiment technique medicine 1. In addition to the 1st 900ml liquid which kept it warm at 37 degrees C beforehand, this was stirred by paddle 50 revolution per minute. It sampled with time, the 1st liquid of the amount of said was added simultaneously, and elution volume was fixed. It measured by HPLC about the sampled liquid, and the rate of elution was computed.

[0050] (2) An experimental result is shown in experimental-result view 1 . Although weight %s of carboxymethylcellulose sodium are 15.8 and 26.5 or 34.1%, respectively, also in any, it is eluted about 100% in 10 minutes, and elution nature understands that it is satisfactory.

[0051] Such a constituent became clear [excelling in the bitterness prevention effect] from the above example of an experiment at this invention. Moreover, since it was uninfluential in the effect even if it passed through the process of tablet-izing of a particle size regulation etc., it became clear that it can consider as dosage forms, such as a granule which is easy to carry out internal use to a child or old people. Furthermore, it was also suggested that the bitterness prevention effect acquired by this invention improves by heat-treating again.

[0052] Furthermore, a constituent may serve as the raw material with a bitterness prevention tablet it is very desirable as a bitterness prevention tablet, and desirable even if such a tablet takes [that the result of an elution test is very good, and] an example by this invention.

[0053]
[Function] To it, the constituent obtained by such constituent or the manufacture technique delays elution of a medicine temporarily to this invention, suppresses the unpleasant taste in the inside of the opening at the time of internal use, and is quickly eluted after that in it.

[Translation done.]

* NOTICES *

Field

[Field of the Invention] this invention relates to the physic constituent which prevents the unpleasant taste of a physic compound, a tablet, and its manufacture technique. Furthermore, it is related with the physic constituent which prevented in detail the unpleasant taste which comes to contain a water soluble polymer and the wax-like matter, tablets, or such manufacture technique.

[Translation done.]

* NOTICES *

Technique

[The background and the conventional technique] of invention Trouble will be caused to obtaining the effect of a medicine for the maximum -- a patient's compliance falls -- if there is an unpleasant taste when carrying out internal use of the medicine, although restricted to neither a child nor old people. Then, making it dosage forms, such as a sugar-coated pill, a film coat lock, and a capsule, and covering and carrying out internal use of the unpleasant taste has been performed from the former. However, it is hard to carry out the deglutition of such a tablet, and is hard to medicate a child and old people with it too. Then, the tablet which covered the unpleasant taste has been strongly desired by the dosage forms which are easy to carry out a deglutition, such as powder and a granule.

[0003] Although a tablet device, such as adding a sweetening agent and perfume, was made in order to suppress the unpleasant taste in the inside of the opening at the time of recipe of powder, a granule, etc. now, suppression of the perfect unpleasant taste was difficult.

[0004] then, although the technique of carrying out the pulverization by the spray ******** method after sharing with the technique or the wax-like matter coated with the microencapsulation of a physic compound and a stomach solubility base material is taken, equipment special to a manufacture in the biological utilization factor of a physic compound falling is required just because it makes masking perfect -- etc. -- it has the fault Moreover, after corning a physic compound and the mixture of the water bloating tendency matter with dry process, the covering tablet which **ed so that the wax-like matter might wear a front face and which carried out bitterness masking is indicated by JP,4-300821,A. However, by this technique, prevention of bitterness was inadequate, and since it was necessary to heat-treat after a granulation and to coat the wax-like matter, there was a fault without the good operability at the time of being a manufacture.

[Translation done.]

* NOTICES *

Effect

[Effect of the Invention] Since the effect of this invention is shown below, the example of an experiment is hung up.
the example 1 of an experiment -- unpleasant -- taste prevention effect (1)7beta-[2-(2-aminothiazole-4-****)-2-(Z)-hydroxyimino acetamide]-3-N and N-dimethyl carbamoyl oxymethyl-3-cephem-carboxylic acid 1-(isopropoxycarbonyloxy) ethyl ester The unpleasant taste (bitterness) prevention effect of a hydrochloride (medicine 1) was examined by the following technique. the place which preceded the exam first, performed the organoleptics of the taste as a preliminary test, and calculated the threshold of bitterness -- about 20microg/ml it was -- from things, when the following exams were also below this concentration, it was judged that there was no bitterness
[0034] (1) The constituent obtained in the example 1 of 50mg considerable amount of the experiment technique medicine 1 - the example 9 was added to 30ml of water, and was shaken by the hand for 10 seconds, it filtered immediately in Millipore (0.45 micrometers), 1ml of this filtrate was diluted with the decinormal hydrochloric acid to 5ml, and determination was performed by HPLC. Based on this result, the concentration of the medicine 1 eluted in the filtrate was calculated. When this concentration was 20micro less thang/ml, although the tablet was included in the opening, it was judged that there was no bitterness. As a contrast, the water bloating tendency matter was used instead of the water soluble polymer, and the granule obtained by the following technique was used.
[0035] (Contrast 1) 20l. super mixer was performed 338g of 484g and light anhydrous silicic acid of a medicine 1, and the granulation was performed by ethanol after mixture for 5 minutes. This was performed at 50 degrees C and the stack type dryer performed the particle size regulation on the 24 mesh screen after xeransis. ********** sugar fatty-acid-ester S-370 (tradename) 11.5g was mixed with 11.5g of this granulatio with the small stirring granulating machine. A granulation container is succeedingly heated at a heater and it stirs in the place which the wax-like matter began to dissolve. When the granulation was completed, the granulation container was cooled, the sieving of the granulation object was carried out, and granulatio 1000 micrometers or less was obtained.
[0036] (Contrast 2) ********** sugar ester S-570 (tradename) was used instead of ********** sugar fatty acid ester S-370, and granulatio was obtained according to the contrast 1.
[0037] (2) An experimental-result experimental result is shown in the following table 1.
[0038]
[Table 1]

実施例No.	1	2	3	4	5
濾液中薬物濃度 (μg/ml)	2.34	7.12	1.88	11.41	7.19

実施例No.	6	7	8	9	12
濾液中薬物濃度 (μg/ml)	3.12	5.62	3.31	7.21	8.28

実施例No.	対照1	対照2
濾液中薬物濃度 (μg/ml)	245.4	459.3

[0039] The tablet of 50mg considerable amount of the example of experiment 2 elution-test (1) (1) experiment technique medicine 1 was added to 40ml of decinormal hydrochloric acids, and it shook with the shaker (200rpm) for 15 minutes, and

filtered immediately in Millipore (0.45 micrometers), 1ml of this filtrate was diluted with the decinormal hydrochloric acid to 10ml, and determination was performed by HPLC. The concentration of a medicine 1 eluted in the filtrate on the basis of this result was calculated.
[0040] (2) The result of the experimental-result above is shown in Table 2.
[0041]
[Table 2]

実施例No.	1	2	3	4	5
溶出率 (%)	12	91	73	106	99

実施例No.	6	7	8	9
溶出率 (%)	95	107	103	103

[0042] The bitterness prevention effect of the example of experiment 3 unpleasant taste prevention effect (2) medicine 2 was examined by the following technique. the place which preceded the exam first, performed the organoleptics of the taste as a preliminary test, and calculated the threshold of bitterness -- about 250microg/ml it was -- from things, when the following exams were also below this concentration, it was judged that there was no bitterness
[0043] (1) The constituent of 50mg considerable amount of the medicine 2 which reaches experiment technique example 10-11 and was obtained by 14 was added to 30ml of water, and it shook with the shaker (a part for 200 times/) for 30 seconds, and filtered immediately in Millipore (0.45micro meter), and determination was performed for this filtrate by HPLC. When this concentration was 250micro less thang/ml, although the tablet was included in the opening, it was judged that there was no bitterness.
[0044] (2) The experimental result of the experimental-result above is shown in the following table 3.
[0045]
[Table 3]

実施例No.	10	11	13	14
濾液中薬物濃度 (μg/ml)	13.0	12.0	6.39	64.0

[0046] The constituent of 50mg considerable amount of the example of experiment 4 elution test (2) medicine 2 was added to 40ml of decinormal hydrochloric acids, and it shook with the shaker (200rpm) for 15 minutes, and filtered immediately in Millipore (0.45 micrometers), 1ml of this filtrate was diluted with 4ml of decinormal hydrochloric acids, and determination was performed by HPLC. The concentration of the medicine 2 eluted in the filtrate based on this result was calculated.
[0047] (2) The result of the experimental-result above is shown in Table 4.
[0048]
[Table 4]

実施例No.	10	11	14
溶出率 (%)	95	83	78

[0049] In the tablet obtained in the example of experiment 5 elution test (3) examples 7-9, the elution test was performed according to technique given in the Pharmacopoea of Japan as follows.
(1) **** correctly the tablet of 150mg considerable amount of the experiment technique medicine 1. In addition to the 1st 900ml liquid which kept it warm at 37 degrees C beforehand, this was stirred by paddle 50 revolution per minute. It sampled with time, the 1st liquid of the amount of said was added simultaneously, and elution volume was fixed. It measured by HPLC about the sampled liquid, and the rate of elution was computed.
[0050] (2) An experimental result is shown in experimental-result view 1 . Although weight %s of carboxymethylcellulose sodium are 15.8 and 26.5 or 34.1%, respectively, also in any, it is eluted about 100% in 10 minutes, and elution nature understands that it is satisfactory.
[0051] Such a constituent became clear [excelling in the bitterness prevention effect] from the above example of an experiment at this invention. Moreover, since it was uninfluential in the effect even if it passed through the process of tablet-izing of a

particle size regulation etc., it became clear that it can consider as dosage forms, such as a granule which is easy to carry out internal use to a child or old people. Furthermore, it was also suggested that the bitterness prevention effect acquired by this invention improves by heat-treating again.

[0052] Furthermore, a constituent may serve as the raw material with a bitterness prevention tablet it is very desirable as a bitterness prevention tablet, and desirable even if such a tablet takes [that the result of an elution test is very good, and] an example by this invention.

[Translation done.]

PDR® entry for

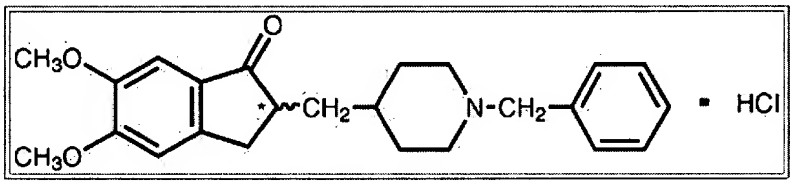
ARICEPT® (Pfizer)
(Donepezil Hydrochloride

Tablets)

Description

DESCRIPTION

ARICEPT ® (donepezil hydrochloride) is a reversible inhibitor of the enzyme acetylcholinesterase, known chemically as (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1 *H* -inden-1-one hydrochloride. Donepezil hydrochloride is commonly referred to in the pharmacological literature as E2020. It has an empirical formula of $C_{24}H_{29}NO_3HCl$ and a molecular weight of 415.96. Donepezil hydrochloride is a white crystalline powder and is freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in acetonitrile and practically insoluble in ethyl acetate and in n-hexane.



ARICEPT ® is available for oral administration in film-coated tablets containing 5 or 10 mg of donepezil hydrochloride. Inactive ingredients are lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. The film coating contains talc, polyethylene glycol, hydroxypropyl methylcellulose and titanium dioxide. Additionally, the 10 mg tablet contains yellow iron oxide (synthetic) as a coloring agent.

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CLINICAL PHARMACOLOGY

Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's Disease attribute some of them to a deficiency of cholinergic neurotransmission.

Donepezil hydrochloride is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its

hydrolysis by acetylcholinesterase. If this proposed mechanism of action is correct, donepezil's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that donepezil alters the course of the underlying dementing process.

Clinical Trial Data

The effectiveness of ARICEPT ® as a treatment for Alzheimer's Disease is demonstrated by the results of two randomized, double-blind, placebo-controlled clinical investigations in patients with Alzheimer's Disease (diagnosed by NINCDS and DSM III-R criteria, Mini-Mental State Examination >/= 10 and </= 26 and Clinical Dementia Rating of 1 or 2). The mean age of patients participating in ARICEPT ® trials was 73 years with a range of 50 to 94. Approximately 62% of patients were women and 38% were men. The racial distribution was white 95%, black 3% and other races 2%.

Study Outcome Measures: In each study, the effectiveness of treatment with ARICEPT ® was evaluated using a dual outcome assessment strategy.

The ability of ARICEPT ® to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's Disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The patients recruited as participants in each study had mean scores on the Alzheimer's Disease Assessment Scale (ADAS-cog) of approximately 26 units, with a range from 4 to 61. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's Disease suggest that they gain 6 to 12 units a year on the ADAS-cog. However, lesser degrees of change are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in ARICEPT ® trials was approximately 2 to 4 units per year.

The ability of ARICEPT ® to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC plus. The CIBIC plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure.

As such, results from a CIBIC plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC plus evaluations from other clinical trials. The CIBIC plus used in ARICEPT ® trials was a semi-structured instrument that was intended to examine four major areas of patient function: General, Cognitive, Behavioral and Activities of Daily Living. It represents the assessment of a skilled clinician based upon his/her observations at an interview with the patient, in combination with information supplied by a caregiver familiar with the behavior of the patient over the interval rated. The CIBIC plus is scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved," to a score of 4, indicating "no change" to a score of 7, indicating "markedly worse." The CIBIC plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

Thirty-Week Study

In a study of 30 weeks duration, 473 patients were randomized to receive single daily doses of placebo, 5 mg/day or 10 mg/day of ARICEPT ®. The 30-week study was divided into a 24-week double-blind active treatment phase followed by a 6-week single-blind placebo washout period. The study was designed to compare 5 mg/day or 10 mg/day fixed doses of ARICEPT ® to placebo. However, to reduce the likelihood of cholinergic effects, the 10 mg/day treatment was started following an initial 7-day treatment with 5 mg/day doses.

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 30 weeks of the study. After 24 weeks of treatment, the mean differences in the ADAS-cog change scores for ARICEPT ® treated patients compared to the patients on placebo were 2.8 and 3.1 units for the 5 mg/day and 10 mg/day treatments, respectively. These differences were statistically significant. While the treatment effect size may appear to be slightly greater for the 10 mg/day treatment, there was no statistically significant difference between the two active treatments.

Following 6 weeks of placebo washout, scores on the ADAS-cog for both the ARICEPT ® treatment groups were indistinguishable from those patients who had received only placebo for 30 weeks. This suggests that the beneficial effects of ARICEPT ® abate over 6 weeks following discontinuation of treatment and do not represent a change in the underlying disease. There was no evidence of a rebound effect 6 weeks after abrupt discontinuation of therapy.

Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment.

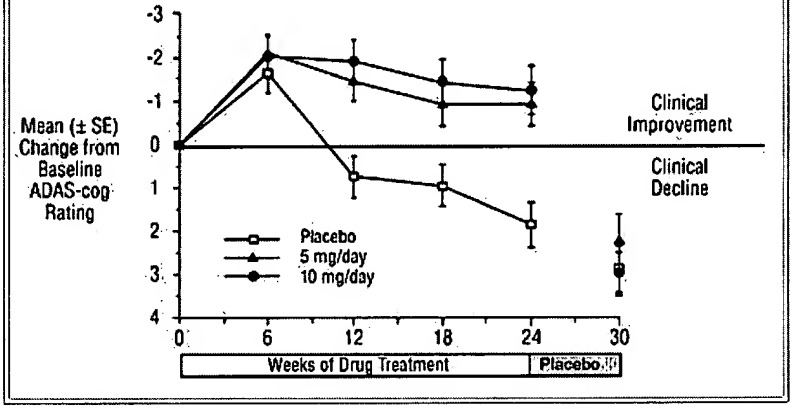

Figure 2 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained the measure of improvement in ADAS-cog score shown on the X axis. Three change scores, (7-point and 4-point reductions from baseline or no change in score) have been identified for illustrative purposes and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to placebo and ARICEPT ® have a wide range of responses, but that the active treatment groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon or shifted to the right of the curve for placebo, respectively.